UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/790,043	01/28/97	PAYNE D	GM50005

HM31/0804

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY UW2220
P O BOX 1539
KING OF PRUSSIA PA 19406-0939

EXAMINER	
PRIEBE,S	

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 08/04/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/790,043	Applicant(s) Payne et al.
	Examiner Scott D. Priebe, Ph.D.	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Jun 29, 1998*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-5, 7-11, and 25-48* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 7-11, 25-28, and 31-48* is/are rejected.

☒ Claim(s) *4, 5, 29, and 30* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

The amendment filed 6/29/98 is acknowledged. Claims 6 and 12-24 have been cancelled. Claims 1, 4, 5, 7 and 10 have been amended, and claims 25-48 have been added. The amendments to the specification at pages 42, 45, 49, 51 and 52 could not be entered; the terms and phrases indicated were not present in the lines indicated. Applicant should use a copy of the of the specification as filed in making amendments; it appears that the copy from which applicant is working is not identical to that filed with respect to the text at any given page and line.

All other amendments were entered as directed. In future amendments, it is requested that unchanged claims not be reproduced in among amended claims. If it is desired to provide a clean copy of all pending claims in a response, it is suggested and urged that it be done in the form of an appendix to the response and clearly indicated as such on each page of such an appendix. Reproducing unchanged claims in among amended claims can be confusing to the printer of the patent and others reviewing the file.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the **first sentence** of the specification (37 CFR 1.78).

The priority information has been inserted after the first paragraph of the specification.

Specification

The disclosure is objected to because of the following informalities: On page 6, line 29, "and 1A" should be deleted, and --and 2A-- should be inserted at line 31 after "Figure 2".

Appropriate correction is required.

Claim Objections

Claims 1, 5, 7, 29 and 30 are objected to because of the following informalities: In claims 1 and 7 part (b), line 1, --of-- should be inserted before. In claims 4, 5, 29 and 30, --isolated-- should be inserted after "The". In claim 5, --a-- should be inserted after "comprising".

Appropriate correction is required.

Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 48 merely recites the definition for "hybridizes under stringent conditions", recited in claim 47 from which it depends, as set forth in the specification at page 17, lines 19-23.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-11, 25-45, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no clear support in the specification as originally filed for calculating sequence similarity using the "default parameters" of any publicly available algorithm, including those specifically recited in claims 1-5, 7-11, 25, 27-45, 47 and 48 or using the algebraic formula recited in claim 26. Thus, there is no indication that such limitations were contemplated at the time the invention was made, and the limitations are new matter.

Claims 1-3 and 7-11 remain rejected and new claims 25, 27, 28, 31-45, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding amino acids 1-256 of SEQ ID NO: 2, does not reasonably provide enablement for polynucleotide sequences having less than 100% identity with the region of such a polynucleotide that encodes amino acids 1-256 of SEQ ID NO: 2, or a part of this coding region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are either drawn to or recite a polynucleotide that has at least 70%, 95% or 97% identity with a reference polynucleotide that encodes SEQ ID NO: 2 or the mature polypeptide expressed by the Fab I gene present in the deposited *S. aureus* strain, which barring sequencing errors should also encode SEQ ID NO: 2. The reference polynucleotides can have as little as 66% sequence identity with each other due to the degeneracy of codon sequences. Therefore a polynucleotide with as little as 70%, 95% or 97% sequence identity over a region corresponding to the coding region of the reference polynucleotide, can have as little as 46% (70% of 66%), 63% or 64% nucleotide sequence identity with a natural *S. aureus* sequence encoding FAB I, such as that set forth as SEQ ID NO: 1. If the 30%, 5% or 3% non-identical nucleotides are present in non-wobble base positions, the resulting polynucleotide would encode a polypeptide with as little sequence identity with SEQ ID NO: 2 as 9%, 85% or 91%, respectfully,

if the differences do not produce stop codons or frame shifts. If the differences produce stop codons or frame shifts, then the polynucleotides may encode no protein at all.

The specification teaches how to use the claimed polynucleotides to make FAB I polypeptides of fragments thereof for making antibodies and for screening assays for compounds that enhance or inhibit the function of FAB I or express a fragment or all of FAB I for therapeutic treatments, e.g. immunization, or to use as hybridization probes for sequences which have at least 95% sequence identity with the probe sequence, presumably natural sequences which encode FAB I or as PCR primers to amplify a natural sequence, such as might be used for a diagnostic assay for the presence of *S. aureus*.

Regardless of the use of the polynucleotides, the uses taught in the specification require that either the nucleotide sequence or amino acid sequence be nearly identical to a natural nucleotide or amino acid sequence of an FAB I protein, mostly the *S. aureus* FAB I given that the claims are limited to the *S. aureus* FAB I sequence as the amino acid sequence encoded by the reference nucleic acid. Where the use requires polynucleotides encoding an active FAB I protein, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, pp. 433 and 492-495). The specification contains no guidance or citations of relevant prior art that would inform the skilled artisan of which amino acid residues of SEQ ID NO: 2 could be altered without adversely affecting its folding or its

biological activity. For polynucleotides encoding a FAB I polypeptide or fragment thereof for inducing an immunological response, such as for the production of antibodies or for immunization, the specification does not teach which fragments of the natural FAB I protein might be sufficiently antigenic or immunogenic for such purposes, but more to the point, how such peptides could be altered by substituting, inserting or deleting amino acids to retain or improve the antigenic or immunogenic properties of the peptide. This latter point is key for claims 11, 38 and 44 which read on a method of making cells *in vivo* and method for making a polypeptide from such cells *in vivo* for producing antibodies against FabI polypeptide. With respect to polynucleotides to serve as probes or primers, the corresponding nucleic acids of *Anabaena, Escherichia, Salmonella, Hemophilus* and *Mycobacterium* bacteria and *Brassica*, a plant, share no more than 56% sequence similarity over the region of nucleotides 440-756, and as taught in the specification (page 3), the overall amino acid sequence identity with the *Escherichia, Salmonella, Mycobacterium* and *Brassica* FAB I proteins share less than 35% sequence identity with the *S. aureus* FAB I. Thus the claimed nucleic acids would not appear to be suitable as hybridization probes for related sequences from Gram negative bacteria, cyanobacteria, or plants. The specification teaches no other class of organisms other than *S. aureus* for which one skilled in the art might expect the claimed polynucleotides to be useful as a probe or primer for FAB I nucleic acids. Neither the specification nor the prior art provides sufficient information to the skilled artisan to determine which among the claimed polynucleotides would be useful for any one of the disclosed uses, i.e. which sequence alterations in SEQ ID NO: 2 would at least preserve the

properties of encoding functional FAB I, encoding antigenic or immunogenic peptides that would bind to a natural FAB I, or alterations of SEQ ID NO: 1 which hybridize effectively with a natural nucleic acid encoding an FAB I protein. To determine which of the high number of sequences encompassed by the claims could be used for the disclosed purposes would require excessive trial and error experimentation. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only a single amino acid sequence and nucleotide sequence having the necessary properties for the disclosed uses. In light of the limited guidance for making polynucleotides having the necessary properties

and the failure of state of the prior art to provide the information missing from the specification, the limited number of working examples, the unpredictable nature of determining the useful sequences *a priori*, the excessive trial and error experimentation that would then be required to identify the useful sequences within the claimed groups of polynucleotides, it would require undue experimentation to make and use the polynucleotides commensurate in scope with the claimed invention for the uses disclosed in the specification.

Applicant's arguments filed 6/29/98 have been fully considered but they are not persuasive. It is asserted on page 14 of the response does not need to know the tertiary structure of any protein encoded by the polynucleotides embraced by the invention because the proteins encoded thereby can be tested for activity. Make and test is not the standard for enablement, see *In re Fisher* (*supra*), and requires excessive trial and error experimentation. It is argued that *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (*supra*) does not apply because the claims set boundaries on the claimed polynucleotides, however, as discussed above, these boundaries are largely illusory and still encompass an inordinate number of permutations. It is argued that what constitutes undue experimentation changes with advances in the art, however no evidence has been supplied that shows that the standard in the art has changed to the extent that it is routine to engage in the excessive amount of trial and error experimentation required to determine which of the thousands of sequences even for polynucleotides that are 97% identical to a reference polynucleotide would encode an active enzyme or an epitope that induces formation of antibodies that would recognize a peptide with a different sequence. With respect to hybridization, the claims do not recite that the

sequence identity relates to SEQ ID NO: 1, but to a polynucleotide encoding SEQ ID NO: 2, which could differ from SEQ ID NO: 1 by as much as 33%. Such a polynucleotide would be of limited use even if a Fab I gene of a different organism encoded the same polypeptide as *S. aureus*, which is extremely unlikely even for other staphylococci. Teaching which embodiments of a broadly claimed genus can be used for the disclosed utilities is an integral part of the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 7-11, 25, 27, 28 and 31-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 7, 25, 34, 39 and 40 and claims dependent thereon are indefinite for recitation of "algorithm with default parameters ... FASTA". While this phrase is definite for any given moment in time, applicant has no control over the default settings of these algorithms, which may be subject to change at any point in the future. Consequently, the metes and bounds of the claimed invention may change over time and are therefore unclear.

Claims 2, 3, 27, 28 recite "The polynucleotide" which lacks proper antecedent basis in the claim since the base claims recite "reference polynucleotide" as well as "isolated polynucleotide". The term --isolated-- should be inserted after "The".

Claims 35 and 41 recite the limitation "the DNA". There is insufficient antecedent basis for this limitation in the claim, rendering these claims and those dependent thereon indefinite.

Claims 46-48 are indefinite for recitation of "hybridizes under stringent conditions". The specification defines "stringent" hybridization conditions in terms of sequence identity. The specification discloses a number of methods for calculating sequence identity without defining the parameters used. These methods do not all yield the same results in part because of the way in which insertion/deletion differences are handled, therefore unless one specific algorithm including parameters is recited, the metes and bounds of the claim are unclear as they arbitrarily depend on the method the skilled artisan would use to determine whether a given polynucleotide fell within the scope of the claimed polynucleotide.

Applicant's arguments filed 6/29/98 have been fully considered but they are not persuasive. The argument provides numerous assertions as to what one of skill in the art would know or not know, interpret or not interpret. These arguments are simply unsupported speculation. The fact remains that the metes and bounds of the polynucleotides embraced by these claims are not defined in the specification, and therefore one skilled in the art cannot be certain whether a specific sequence is embraced or not.

Double Patenting

Applicant is advised that should claims 4 and 5 be found allowable, claims 29 and 30 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Allowable Subject Matter

Claims 4 and 5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, Ph.D., can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SDP

Scott D. Priebe, Ph.D.
Patent Examiner
Art Unit 1632

August 3, 1998

Jasemine C. Chambers

Jasemine C. Chambers
Supervisory Patent Examiner
Technology Center 1600